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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: David E. Fisher

Application No.: 09/229,283 Group No.: 1642

Filed: 1/13/1999 Examiner: UNGAR, Susan

For: USE OF MICROPHTHALMIA FOR DIAGNOSIS, PROGNOSIS AND/OR TREATMENT OF MELANOMA

DECLARATION OF DAVID E. FISHER

I, David E. Fisher, hereby declare as follows:

1. I am Director of the Melanoma Program, Department of Medical Oncology and Department of Pediatric Hematology/Oncology at the Dana-Farber Cancer Institute, Inc., Boston, MA.

2. I am Associate Professor at the Harvard Medical School, Boston, MA.

3. I am also the inventor of the above-described application.

4. I am familiar with the comments raised by the U.S. Patent Office in an Office Action mailed August 19, 2003.

5. I disagree with the conclusions made by the Examiner for the following reasons.

6. I taught a method for diagnosing melanoma that involved contacting a biological sample containing malignant cells with a probe that recognizes microphthalmia. At the time of the patent application, we were abbreviating that name as Mi. Since that time, the protein has been called microphthalmia-associated transcription factor abbreviated MiTF or MITF. I taught that the skilled artisan, typically a pathologist, could diagnose melanoma by taking a specimen containing malignant cells and using probes that bind to Mi where the expression of Mi in a

malignant cell is indicative of melanoma. Thus, the claim specifically teaches the skilled artisan not to just look for the expression of MiTF, but for the expression of MiTF in a malignant cell. Although not explicitly stated people in the field understand that when using a probe they cannot just use it in isolation. They have to use it with what their training has brought to the field. As we teach in our application, the probe can be an antibody (immunohistochemistry) or the probe can be a probe that detects the present of mRNA.

7. The use of antibodies is one of the most important methods of providing malignancy diagnostics. That value of immunohistochemistry is recognized in Chapter 13 of the textbook Cancer: Principles in Practice of Oncology, Fourth Edition, edited by DeVita, V., Hellman, S. and Rosenberg, S. (copyright 1993), wherein the text states at page 231:

> The immunohistochemical method has contributed more than any other special technique to the histopathologic diagnosis of tumors.

The chapter goes on to state that the specificity of antibodies adds very useful information to the **collective body of data** which a pathologist employs in arriving at a diagnosis. Namely, the skilled artisan does not look at a single point in isolation. For example, in being directed to determine expression of Mi in a malignant cell, the skilled artisan would know that they must use other available criteria in looking at a specimen to identify the malignant cell expressing MiTF (Mi).

8. The Examiner stated that osteoclasts, mast cells and melanocytes, which also express MiTF, might also be present in samples. This would not cause any problem because the skilled artisan would know that osteoclasts are multinucleated whereas melanoma cells have only one nucleus; mast cells are filled with basophilic granules whereas melanoma are not; and melanocytes are not invasive cells whereas melanoma cells are. Thus, by looking at the specimen, the skilled artisan would be able to distinguish which cells express Mi in malignant cells and not

be bothered by the potential presence of osteoclasts, mast cells and melanocytes. Moreover, osteoclasts and mast cells are among the rarest cells in the body so the likelihood of their appearing in a specimen is extremely low. Nevertheless, there would be no ambiguity between osteoclasts, mast cells and melanocytes as opposed to a melanoma cell to the skilled artisan, i.e., a pathologist. It should be remembered that in pathology when one is talking about diagnosis what one is doing is narrowing the list of things that could potentially satisfy the diagnosis. One is not necessarily talking about 100% certainty, and the skilled artisan would recognize that because we stated that the expression of Mi in a malignant cell is **indicative** of melanoma.

9. The Examiner also discusses at page 3 of the Office Action that "although a review of Figure 6 [of my application] reveals differential staining of melanoma in situ as compared to normal control, not only malignant cells but also benign nevus and dysplastic nevus cells which are not malignant" show staining. Again, the person skilled in the art would not be confused and would not identify such cells as being malignant. The reason for this is that differentiating melanoma from benign melanocyte lesions requires no antibody. When a specimen is brought out of the operating room, pathologists routinely look at cells to determine whether they are malignant or benign using certain standard stains. We talk about looking for expression of Mi in a malignant cell. The skilled pathologist knows how to differentiate a malignant cell from a non-malignant cell and routinely does so. This is standard practice.

10. My application expressly talks about diagnosing melanoma by stating that the expression of Mi in the malignant cell is indicative of melanoma. The Examiner states that the application does not teach distinguishing melanoma from other tumors. I disagree. First, we are stating that the expression of Mi in a malignant cell is indicative of melanoma. As the artisan knows and as the word "indicative" indicates, I am not talking about absolute 100% certainties.

None of the current markers on the market give absolute certainties. As I will discuss below, I believe the research confirms that this marker is extremely good at distinguishing melanoma from other tumors – better than the markers that were being used at the time. Therefore, the Examiner's statement that two non-melanoma tumors were found to stain positive for Mi would be of no consequence to the skilled artisan.

11. Indeed, I find the Examiner's discussion of the two non-melanoma tumors somewhat out of context. We indicated explicitly at that point that Mi stains cytoplasm in two of 81 cases and in no cases was there nuclear staining. Thus, in only 2 out of 81 non-melanomic malignant cases, in only about 2.5%, was there any staining, and the staining was in the cytoplasm not the nucleus.

12. Further, on page 232 in Chapter 13 of textbook discussed above, several particularly valuable antibody diagnostics are discussed. Included among these examples are S-100 and HMB-45. As stated in the text, both of these standard diagnostic reagents are imperfect in their sensitivity and specificity, yet, nonetheless are extremely valuable for cancer diagnosis. This text was written prior to our invention.

13. In fact, in the present application in Figures 7, 8 and Table 1 and the discussion at pages 25 through 27, a comparison is made between the present method of using an MiTF probe relative to S-100 and HMB-45. As shown, our probe was more sensitive and more specific than either of those other two antibodies which are nonetheless cited as standard and valuable diagnostic reagents in the text cited above.

14. Just as we taught in the application, people have found that the use of a probe for MiTF is extremely useful. See Chang, K.L. and Folpe, A.L., Advances in Anatomic Pathology, 8:273-275 (2001).

15. The Examiner has contended that we have not addressed the ability of an Mi probe to discriminate between the isoforms. We taught that one should use a probe for Mi and that such a probe will work. The fact that certain isoforms may be found in different places does not affect our teaching. Namely, that the presence of Mi in a malignant cell is indicative of melanoma. With respect to specific antibodies, we are discussing probes that selectively recognize the expression of Mi. Given the teaching and the exemplification of the type of results obtained in the examples, one can readily determine if one has obtained the appropriate antibody.

16. With respect to the question of whether or not one can diagnose melanoma with a probe that detects the presence of mRNA expressing Mi in malignant cells, we taught that you could. The Examiner contends that there are examples where protein levels do not correlate with steady state RNA levels or alterations in mRNA levels. However, that was not what we taught. In fact in the majority of cases, protein and RNA expression levels do correlate, and as in the majority of cases, mRNA levels of MiTF and protein expression levels do indeed correlate. This is explicitly confirmed at page 334 left-hand column of Du, J. AJP, 163:333-343 (2003) ("Protein and mRNA levels of the three antigens [MITF, SILV and MLANA] were found to correlate in a panel of melanoma cell culture lines as well as human primary melanocytes.") Consequently, as we taught, one can use a probe that looks at mRNA expression levels of Mi.

17. Finally, we wish to emphasize that one of the problems that occurs in recognizing melanomas from other malignant cells is that many melanomas lose pigmentation particularly as they progress and metastasize. Thus, these tumors represent significant diagnostic dilemmas. I found and taught that by contacting a biological specimen containing malignant cells with a probe for MiTF the skilled artisan can then determine the presence (or conversely, the absence) of Mi in such malignant cells and the results can be diagnostic for cancer. If it is present in the malignant

cell, it is indicative of the cells origin, and it is a melanoma. We believe that the method we teach can readily be practiced as taught by the skilled artisan.

18. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

David E. Fisher